10/037,519
Cook 6/30/05

ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1997:314054 BIOSIS
DN PREV199799604542
TI Stopped-flow kinetics reveal multiple phases of **thioflavin T** binding to Alzheimer beta(1-40) amyloid fibrils.
AU Levine, Harry Iii
CS Neurodegenerative Diseases, Parke-Davis Pharmaceutical Research Div., Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, MI 48105-1047, USA
SO Archives of Biochemistry and Biophysics, (1997) Vol. 342, No. 2, pp. 306-316.
CODEN: ABBIA4. ISSN: 0003-9861.
DT Article
LA English
ED Entered STN: 26 Jul 1997
Last Updated on STN: 4 Sep 1997
AB The benzothiazole dye **thioflavin T** (ThT) is a classical amyloid stain for senile plaques containing beta/A4 peptide in Alzheimer's disease brain. ThT also binds rapidly and specifically to the anti-parallel beta-sheet fibrils formed from **synthetic** beta(1-40) peptide, but does not bind to monomer or oligomeric intermediates. The fibrillar beta-sheet-bound dye species undergoes a characteristic 120 **nm** red shift of its excitation spectrum that may be selectively excited at 450 **nm**, resulting in a fluorescence signal at 482 **nm**. Mixing of preformed beta(1-40) amyloid fibrils with ThT in a stopped-flow spectrophotometer, monitoring fluorescence emission at gt 475 **nm** while exciting at 450 **nm**, distinguished multiple kinetic phases of roughly equivalent amplitude with tau's in the ranges of 0.007, 0.05, 0.75, and 10-20 s. The fastest reaction appears to reflect a bimolecular dye binding event while the remaining reactions are rate-limited by protein tertiary or quaternary conformational changes. The high activation energies of the three slower reactions support this interpretation. The ThT concentration dependence of the reaction rates at different ratios of ThT/beta(1-40) amyloid fibrils rules out a rate-limiting conformational change occurring prior to ligand binding. ThT is a useful probe for the **aggregated** fibrillar state of beta(1-40) amyloid fibrils as the amyloid-specific fluorescence reports only fibrillar species. The binding of ThT does not interfere with the **aggregation** of this peptide into amyloid fibrils. The putative conformational changes detected by the ThT fluorescence suggest that small pharmacologic ligands can perturb and possibly dissociate A-beta amyloid fibrils.
CC Biochemistry studies - General 10060
Biophysics - General 10502
Nervous system - General and methods 20501
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
THIOFLAVIN; AMYLOID
IT Time
Quaternary; Tertiary
IT Miscellaneous Descriptors
ACTIVATION ENERGY; ALZHEIMER BETA(1-40) AMYLOID FIBRILS; ALZHEIMER'S DISEASE; BEHAVIORAL AND MENTAL DISORDERS; BIOCHEMISTRY AND BIOPHYSICS; BRAIN; CONFORMATIONAL CHANGES; KINETIC PHASES; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; PHARMACOLOGIC LIGANDS; RATE-LIMITING; STOPPED-FLOW KINETICS; **THIOFLAVIN T** BINDING
RN 2390-54-7 (THIOFLAVIN)
11061-24-8 (AMYLOID)

ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:444464 CAPLUS
DN 119:44464
ED Entered STN: 07 Aug 1993
TI **Thioflavin T** interaction with **synthetic** Alzheimer's disease β-amyloid peptides: Detection of amyloid **aggregation** in solution
AU LeVine, Harry, III
CS Dep. Neurosci. Pharmacol., Warner-Lambert Co., Ann Arbor, MI, 48106-1047, USA
SO Protein Science (1993), 2(3), 404-10
CODEN: PRCIEI; ISSN: 0961-8368
DT Journal
LA English
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 14
AB Thioflavine T (ThT) assocs. rapidly with **aggregated** fibrils of the **synthetic** β/A4-derived peptides β(1-28) and β(1-40), giving rise to a new excitation (ex) (absorption) maximum at 450 **nm** and enhanced emission (em) at 482 **nm**, as opposed to the 385 **nm** (ex) and 445 **nm** (em) of the free dye. This change is dependent on the **aggregated** state as monomeric or dimeric peptides do not react, and guanidine dissociation of **aggregates** destroys the signal. There was no effect of high salt concns. Binding to the β(1-40) is of lower affinity, Kd 2 μM, while it sats. with a Kd of 0.54 μM for β(1-28). Insulin fibrils converted to a β-sheet conformation fluoresce intensely with ThT. A variety of polyhydroxy, polyanionic, or polycationic materials fail to interact or impede interaction with the amyloid peptides. This fluorometric technique should allow the kinetic elucidation of the amyloid fibril assembly process as well as the testing of agents that might modulate their assembly or disassembly.
ST thioflavine T amyloid protein fluorescence Alzheimer
IT Mental disorder
(Alzheimer's disease, pathogenesis of, amyloid fibril formation in, thioflavine T interaction with **synthetic** β-amyloid protein-derived peptide fragments studied by fluorometry in relation to)
IT Proteins, specific or class
RL: ANST (Analytical study)
(amyloid A4, **synthetic** peptides derived from, thioflavine T interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)
IT 2390-54-7, Thioflavine T
RL: ANST (Analytical study)
(**synthetic** β-amyloid peptide interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)

10/037,519
LYCook 6/30/05

```
=> s (thioflavin T)
L1          1352 (THIOFLAVIN T)

=> s l1 and 485?
TERM '485?' EXCEEDED TRUNCATION LIMITS - SEARCH ENDED
You have entered a truncated stem which occurs in too many terms.
Make the stem longer and try again.  For example, if your original
term was 'degr?' to search for variations and the abbreviation for
'degradation', you could replace it with the expression '(degrdn OR
degrad?)'.  If your search term was numeric, e.g., 'C>5', reduce the
size of the range.

=> s l1 and aggregat?
L2          611 L1 AND AGGREGAT?

=> s l2 and nm?
L3          121 L2 AND NM?

=> duplicate remove l3
DUPLICATE PREFERENCE IS 'BIOSIS, CAPLUS, EMBASE, MEDLINE, CANCERLIT'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L3
L4            45 DUPLICATE REMOVE L3 (76 DUPLICATES REMOVED)

=> s l4 and syn?
L5            12 L4 AND SYN?

=> d l5 1-12 all

L5   ANSWER 1 OF 12  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
AN   2003:513254  BIOSIS
DN   PREV200300516592
TI   Environmental influences on bovine kappa-casein: Reduction and conversion
     to fibrillar (amyloid) structures.
AU   Farrell, Harold M. Jr. [Reprint Author]; Cooke, Peter H.; Wickham, Edward
     D.; Piotrowski, Edwin G.; Hoagland, Peter D.
CS   Eastern Regional Research Center, United States Department of Agriculture,
     ARS, 600 E. Mermaid Lane, Wyndmoor, PA, 19038, USA
     hfarrell@arserrc.gov
SO   Journal of Protein Chemistry, (April 2003) Vol. 22, No. 3, pp. 259-273.
     print.
     ISSN: 0277-8033 (ISSN print).
DT   Article
LA   English
ED   Entered STN: 5 Nov 2003
     Last Updated on STN: 5 Nov 2003
AB   The caseins of milk form a unique calcium-phosphate transport complex that
     provides these necessary nutrients to the neonate.  The colloidal
     stability of these particles is primarily the result of kappa-casein.  As
     purified from milk, this protein occurs as spherical particles with a
     weight average molecular weight of 1.18 million.  The protein exhibits a
     unique disulfide bonding pattern, which (in the absence of reducing
     agents) ranges from monomer to octamers and above on SDS-PAGE.  Severe
     heat treatment of the kappa-casein (90degreeC) in the absence of SDS,
     before electrophoresis, caused an increase in the polymeric distribution:
     up to 40% randomly aggregated high-molecular weight polymers,
     presumably promoted by free sulfhydryl groups (J.  Protein Chemical 17:
     73-84, 1998).  To ascertain the role of the sulfhydryl groups, the protein
     was reduced and carboxymethylated (RCM-kappa).  Surprisingly, at only
     37degreeC, the RCM-kappa-casein exhibited an increase in weight average
     molecular weight and tendency to self-association when studied at 3000 rpm
     by analytical ultracentrifugation.  Electron microscopy (EM) of the
     37degreeC RCM sample showed that, in addition to the spherical particles
```

```
=> s (thioflavin T)
L1          1352 (THIOFLAVIN T)

=> s l1 and 485?
TERM '485?' EXCEEDED TRUNCATION LIMITS - SEARCH ENDED
You have entered a truncated stem which occurs in too many terms.
Make the stem longer and try again.  For example, if your original
term was 'degr?' to search for variations and the abbreviation for
'degradation', you could replace it with the expression '(degrdn OR
degrad?)'.  If your search term was numeric, e.g., 'C>5', reduce the
size of the range.

=> s l1 and aggregat?
L2          611 L1 AND AGGREGAT?

=> s l2 and nm?
L3          121 L2 AND NM?

=> duplicate remove l3
DUPLICATE PREFERENCE IS 'BIOSIS, CAPLUS, EMBASE, MEDLINE, CANCERLIT'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L3
L4            45 DUPLICATE REMOVE L3 (76 DUPLICATES REMOVED)

=> s l4 and syn?
L5           12 L4 AND SYN?

=> d l5 1-12 all

L5   ANSWER 1 OF 12  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
AN   2003:513254  BIOSIS
DN   PREV200300516592
TI   Environmental influences on bovine kappa-casein: Reduction and conversion
     to fibrillar (amyloid) structures.
AU   Farrell, Harold M. Jr. [Reprint Author]; Cooke, Peter H.; Wickham, Edward
     D.; Piotrowski, Edwin G.; Hoagland, Peter D.
CS   Eastern Regional Research Center, United States Department of Agriculture,
     ARS, 600 E. Mermaid Lane, Wyndmoor, PA, 19038, USA
     hfarrell@arserrc.gov
SO   Journal of Protein Chemistry, (April 2003) Vol. 22, No. 3, pp. 259-273.
     print.
     ISSN: 0277-8033 (ISSN print).
DT   Article
LA   English
ED   Entered STN: 5 Nov 2003
     Last Updated on STN: 5 Nov 2003
AB   The caseins of milk form a unique calcium-phosphate transport complex that
     provides these necessary nutrients to the neonate.  The colloidal
     stability of these particles is primarily the result of kappa-casein.  As
     purified from milk, this protein occurs as spherical particles with a
     weight average molecular weight of 1.18 million.  The protein exhibits a
     unique disulfide bonding pattern, which (in the absence of reducing
     agents) ranges from monomer to octamers and above on SDS-PAGE.  Severe
     heat treatment of the kappa-casein (90degreeC) in the absence of SDS,
     before electrophoresis, caused an increase in the polymeric distribution:
     up to 40% randomly aggregated high-molecular weight polymers,
     presumably promoted by free sulfhydryl groups (J.  Protein Chemical 17:
     73-84, 1998).  To ascertain the role of the sulfhydryl groups, the protein
     was reduced and carboxymethylated (RCM-kappa).  Surprisingly, at only
     37degreeC, the RCM-kappa-casein exhibited an increase in weight average
     molecular weight and tendency to self-association when studied at 3000 rpm
     by analytical ultracentrifugation.  Electron microscopy (EM) of the
     37degreeC RCM sample showed that, in addition to the spherical particles
```

found in the native protein, there was a high proportion of fibrillar structures. The fibrillar structures were up to 600 **nm** in length. Circular dichroism (CD) spectroscopy was used to investigate the temperature-induced changes in the secondary structure of the native and RCM-kappa-caseins. These studies indicate that there was little change in the distribution of secondary structural elements during this transition, with extended strand and beta turns predominating. On the basis of three-dimensional molecular modeling predictions, there may exist a tyrosine-rich repeated sheet-turn-sheet motif in kappa-casein (residues 15-65), which may allow for the stacking of the molecules into fibrillar structures. Previous studies on amyloid proteins have suggested that such motifs promote fibril formation, and near-ultraviolet CD and **thioflavin-T** binding studies on RCM-kappa-casein support this concept. The results are discussed with respect to the role that such fibrils may play in the **synthesis** and secretion of casein micelles in lactating mammary gland.

CC Biochemistry studies - General 10060
Reproductive system - Physiology and biochemistry 16504

IT Major Concepts
Biochemistry and Molecular Biophysics; Reproductive System (Reproduction)

IT Parts, Structures, & Systems of Organisms
mammary gland: reproductive system; milk: reproductive system

IT Chemicals & Biochemicals
kappa-casein: reduction, structure

IT Methods & Equipment
carboxymethylation: laboratory techniques; circular dichroism spectroscopy: laboratory techniques, spectrum analysis techniques; electron microscopy: imaging and microscopy techniques, laboratory techniques; electrophoresis: electrophoretic techniques, laboratory techniques; heat treatment: laboratory techniques; molecular modeling: mathematical and computer techniques; reduction reaction: laboratory techniques; ultracentrifugation: laboratory techniques

IT Miscellaneous Descriptors
kappa-casein fibril; lactation; temperature

ORGN Classifier
Bovidae 85715
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
bovine (common)
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

L5 ANSWER 2 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 2003:394261 BIOSIS

DN PREV200300394261

TI **Synthesis** and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents.

AU Mathis, Chester A. [Reprint Author]; Wang, Yanming; Holt, Daniel P.; Huang, Guo-feng; Debnath, Manik L.; Klunk, William E.

CS PET Facility, UPMC Presbyterian, 200 Lothrop Street, B-938, Pittsburgh, PA, 15213-2582, USA
mathisca@msx.upmc.edu

SO Journal of Medicinal Chemistry, (June 19 2003) Vol. 46, No. 13, pp. 2740-2754. print.
ISSN: 0022-2623 (ISSN print).

DT Article

LA English

ED Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003

AB The **synthesis** and evaluation of a series of neutral analogues of

found in the native protein, there was a high proportion of fibrillar structures. The fibrillar structures were up to 600 **nm** in length. Circular dichroism (CD) spectroscopy was used to investigate the temperature-induced changes in the secondary structure of the native and RCM-kappa-caseins. These studies indicate that there was little change in the distribution of secondary structural elements during this transition, with extended strand and beta turns predominating. On the basis of three-dimensional molecular modeling predictions, there may exist a tyrosine-rich repeated sheet-turn-sheet motif in kappa-casein (residues 15-65), which may allow for the stacking of the molecules into fibrillar structures. Previous studies on amyloid proteins have suggested that such motifs promote fibril formation, and near-ultraviolet CD and **thioflavin-T** binding studies on RCM-kappa-casein support this concept. The results are discussed with respect to the role that such fibrils may play in the **synthesis** and secretion of casein micelles in lactating mammary gland.

CC Biochemistry studies - General 10060
Reproductive system - Physiology and biochemistry 16504

IT Major Concepts
Biochemistry and Molecular Biophysics; Reproductive System (Reproduction)

IT Parts, Structures, & Systems of Organisms
mammary gland: reproductive system; milk: reproductive system

IT Chemicals & Biochemicals
kappa-casein: reduction, structure

IT Methods & Equipment
carboxymethylation: laboratory techniques; circular dichroism spectroscopy: laboratory techniques, spectrum analysis techniques; electron microscopy: imaging and microscopy techniques, laboratory techniques; electrophoresis: electrophoretic techniques, laboratory techniques; heat treatment: laboratory techniques; molecular modeling: mathematical and computer techniques; reduction reaction: laboratory techniques; ultracentrifugation: laboratory techniques

IT Miscellaneous Descriptors
kappa-casein fibril; lactation; temperature

ORGN Classifier
Bovidae 85715
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
bovine (common)
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

L5 ANSWER 2 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:394261 BIOSIS
DN PREV200300394261
TI **Synthesis** and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents.
AU Mathis, Chester A. [Reprint Author]; Wang, Yanming; Holt, Daniel P.; Huang, Guo-feng; Debnath, Manik L.; Klunk, William E.
CS PET Facility, UPMC Presbyterian, 200 Lothrop Street, B-938, Pittsburgh, PA, 15213-2582, USA
mathisca@msx.upmc.edu
SO Journal of Medicinal Chemistry, (June 19 2003) Vol. 46, No. 13, pp. 2740-2754. print.
ISSN: 0022-2623 (ISSN print).
DT Article
LA English
ED Entered STN: 27 Aug 2003
Last Updated on STN: 27 Aug 2003
AB The **synthesis** and evaluation of a series of neutral analogues of

**thioflavin-T** (termed BTA's) with high affinities for **aggregated** amyloid and a wide range of lipophilicities are reported. Radiolabeling with high specific activity (11C)methyl iodide provided derivatives for in vivo evaluation. Brain entry in control mice and baboons was high for nearly all of the analogues at early times after injection, but the clearance rate of radioactivity from brain tissue varied by more than 1 order of magnitude. Upon the basis of its rapid clearance from normal mouse and baboon brain tissues, (N-methyl-11C)2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (or (11C)6-OH-BTA-1) was selected as the lead compound for further evaluation. The radiolabeled metabolites of (11C)6-OH-BTA-1 were polar and did not enter brain. The binding affinities of (N-methyl-3H)6-OH-BTA-1 for homogenates of postmortem AD frontal cortex and **synthetic** Abeta(1-40) fibrils were similar (Kd=1.4 **nM** and 4.7 **nM**, respectively), but the ligand-to-Abeta peptide binding stoichiometry was apprx400-fold higher for AD brain than Abeta(1-40) fibrils. Staining of AD frontal cortex tissue sections with 6-OH-BTA-1 indicated the selective binding of the compound to amyloid plaques and cerebrovascular amyloid. The encouraging in vitro and in vivo properties of (11C)6-OH-BTA-1 support the choice of this derivative for further evaluation in human subject studies of brain Abeta deposition.

CC Behavioral biology - Human behavior 07004
Pathology - Diagnostic 12504
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005

IT Major Concepts
Methods and Techniques; Nervous System (Neural Coordination); Pharmacology

IT Parts, Structures, & Systems of Organisms
brain: nervous system; frontal cortex: nervous system

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Chemicals & Biochemicals
amyloid-beta; carbon-11-labeled 6-substituted 2-arylbenzothiazole: diagnostic-drug, imaging agent, **synthesis**

IT Methods & Equipment
radiolabeling: laboratory techniques

IT Miscellaneous Descriptors
amyloid plaques; amyloid-beta(1-40) fibril; cerebrovascular amyloid

ORGN Classifier
Cercopithecidae 86205
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Papio anubis (species) [baboon (common)]
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Mammals, Nonhuman Vertebrates, Nonhuman Primates, Primates, Vertebrates

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier

**thioflavin-T** (termed BTA's) with high affinities for **aggregated** amyloid and a wide range of lipophilicities are reported. Radiolabeling with high specific activity (11C)methyl iodide provided derivatives for in vivo evaluation. Brain entry in control mice and baboons was high for nearly all of the analogues at early times after injection, but the clearance rate of radioactivity from brain tissue varied by more than 1 order of magnitude. Upon the basis of its rapid clearance from normal mouse and baboon brain tissues, (N-methyl-11C)2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (or (11C)6-OH-BTA-1) was selected as the lead compound for further evaluation. The radiolabeled metabolites of (11C)6-OH-BTA-1 were polar and did not enter brain. The binding affinities of (N-methyl-3H)6-OH-BTA-1 for homogenates of postmortem AD frontal cortex and **synthetic** Abeta(1-40) fibrils were similar (Kd=1.4 **nM** and 4.7 **nM**, respectively), but the ligand-to-Abeta peptide binding stoichiometry was apprx400-fold higher for AD brain than Abeta(1-40) fibrils. Staining of AD frontal cortex tissue sections with 6-OH-BTA-1 indicated the selective binding of the compound to amyloid plaques and cerebrovascular amyloid. The encouraging in vitro and in vivo properties of (11C)6-OH-BTA-1 support the choice of this derivative for further evaluation in human subject studies of brain Abeta deposition.

CC Behavioral biology - Human behavior 07004
Pathology - Diagnostic 12504
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology; psychodynamics and therapy 21002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005

IT Major Concepts
Methods and Techniques; Nervous System (Neural Coordination); Pharmacology

IT Parts, Structures, & Systems of Organisms
brain: nervous system; frontal cortex: nervous system

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Chemicals & Biochemicals
amyloid-beta; carbon-11-labeled 6-substituted 2-arylbenzothiazole: diagnostic-drug, imaging agent, **synthesis**

IT Methods & Equipment
radiolabeling: laboratory techniques

IT Miscellaneous Descriptors
amyloid plaques; amyloid-beta(1-40) fibril; cerebrovascular amyloid

ORGN Classifier
Cercopithecidae 86205
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Papio anubis (species) [baboon (common)]
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Mammals, Nonhuman Vertebrates, Nonhuman Primates, Primates, Vertebrates

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier

Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L5 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:267944 BIOSIS
DN PREV200300267944
TI METAL - DEPENDENCE OF A beta OLIGOMERIZATION.
AU Huang, X. [Reprint Author]; Moir, R. D.; Friedlich, A. L. [Reprint Author]; Nagano, S. [Reprint Author]; Goldstein, L. E. [Reprint Author]; Rogers, J. T. [Reprint Author]; Tanzi, R. E.; Bush, A. I. [Reprint Author]
CS Psychiatry/Genetics and Aging Research Unit, MGH/ Harvard Medical School, Charlestown, MA, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 19.1. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003
AB Introduction: Recent studies have demonstrated that diffusible human A oligomers, i.e. Abeta-derived diffusible ligands (ADDLs) are neurotoxic. It is known that iron, copper, and zinc are highly enriched in amyloid plaques. We have previously found that these metal ions are involved in maintaining the assembly of Abeta amyloid in vitro, and in post-mortem Alzheimer Disease (AD) brain specimens. We recently discovered that treatment with BBB-permeable metal chelator-clioquinol (CQ) inhibited Abeta deposition in APP2576 transgenic mice. Here we study the effects of these metal ions and CQ upon the Abeta oligomerization process used to form ADDLs. Methods: Metal concentrations in cold F12 medium were determined by ICP-MS. Abeta40 and Abeta42 (10 muM) in cold F12 medium were co-incubated at 4C 5 muM CQ or DTPA (another potent chelator). Turbidity readings (400 **nm**) were taken daily over ten days. At the time point where turbidity values plateaued, Abeta **aggregation** was quantified by Congo-Red and **Thioflavin-T** assays. The ADDLs were appraised by protein gel staining and FPLC. Results and Conclusion: The medium was found to contain 0.3 muM of copper, 16 muM of zinc, and 34 muM of iron. We observed the attenuation of Abeta oligomerization by both CQ and DTPA. Hence, the formation of ADDLs is induced by the presence of these metal ions in the medium. Specific metal chelators may be therapeutic for AD in interdicting **synaptotoxic** Abeta oligomerization.
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Minerals 10069
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
IT Major Concepts
Nervous System (Neural Coordination)
IT Diseases
Alzheimer disease: behavioral and mental disorders, nervous system disease, therapy
Alzheimer Disease (MeSH)
IT Chemicals & Biochemicals
A-beta [amyloid-beta]: **synaptotoxic**, deposition,

Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L5 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:267944 BIOSIS
DN PREV200300267944
TI METAL - DEPENDENCE OF A beta OLIGOMERIZATION.
AU Huang, X. [Reprint Author]; Moir, R. D.; Friedlich, A. L. [Reprint Author]; Nagano, S. [Reprint Author]; Goldstein, L. E. [Reprint Author]; Rogers, J. T. [Reprint Author]; Tanzi, R. E.; Bush, A. I. [Reprint Author]
CS Psychiatry/Genetics and Aging Research Unit, MGH/ Harvard Medical School, Charlestown, MA, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 19.1. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003
AB Introduction: Recent studies have demonstrated that diffusible human A oligomers, i.e. Abeta-derived diffusible ligands (ADDLs) are neurotoxic. It is known that iron, copper, and zinc are highly enriched in amyloid plaques. We have previously found that these metal ions are involved in maintaining the assembly of Abeta amyloid in vitro, and in post-mortem Alzheimer Disease (AD) brain specimens. We recently discovered that treatment with BBB-permeable metal chelator-clioquinol (CQ) inhibited Abeta deposition in APP2576 transgenic mice. Here we study the effects of these metal ions and CQ upon the Abeta oligomerization process used to form ADDLs. Methods: Metal concentrations in cold F12 medium were determined by ICP-MS. Abeta40 and Abeta42 (10 muM) in cold F12 medium were co-incubated at 4C 5 muM CQ or DTPA (another potent chelator). Turbidity readings (400 **nm**) were taken daily over ten days. At the time point where turbidity values plateaued, Abeta **aggregation** was quantified by Congo-Red and **Thioflavin-T** assays. The ADDLs were appraised by protein gel staining and FPLC. Results and Conclusion: The medium was found to contain 0.3 muM of copper, 16 muM of zinc, and 34 muM of iron. We observed the attenuation of Abeta oligomerization by both CQ and DTPA. Hence, the formation of ADDLs is induced by the presence of these metal ions in the medium. Specific metal chelators may be therapeutic for AD in interdicting **synaptotoxic** Abeta oligomerization.
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Minerals 10069
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
IT Major Concepts
Nervous System (Neural Coordination)
IT Diseases
Alzheimer disease: behavioral and mental disorders, nervous system disease, therapy
Alzheimer Disease (MeSH)
IT Chemicals & Biochemicals
A-beta [amyloid-beta]: **synaptotoxic**, deposition,

oligomerization; A-beta 40 [amyloid-beta 40]; A-beta 42 [amyloid-beta 42]; DTPA; F12: medium; amyloid beta-derived diffusible ligand [ADDL]; clioquinol: chelating agent; copper; iron; zinc

IT Miscellaneous Descriptors
turbidity reading

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 67-43-6 (DTPA)
130-26-7 (clioquinol)
7440-50-8 (copper)
7439-89-6 (iron)
7440-66-6 (zinc)

L5 ANSWER 4 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:48300 BIOSIS
DN PREV200300048300
TI IMPY: An improved **thioflavin-T** derivative for in vivo labeling of beta-amyloid plaques.
AU Kung, Mei-Ping [Reprint Author]; Hou, Catherine; Zhuang, Zhi-Ping; Zhang, Bin; Skovronsky, Daniel; Trojanowski, John Q.; Lee, Virginia M.-Y.; Kung, Hank F.
CS Department of Radiology, University of Pennsylvania, 3700 Market Street, Room 305, Philadelphia, PA, 19104, USA
kungmp@sunmac.spect.upenn.edu
SO Brain Research, (29 November 2002) Vol. 956, No. 2, pp. 202-210. print.
ISSN: 0006-8993 (ISSN print).
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB Development of small molecular probes for in vivo labeling and detection of beta-amyloid (Abeta) plaques in patients of Alzheimer's disease (AD) is of significant scientific interest, and it may also assist the development of drugs targeting Abeta plaques for treatment of AD. A novel probe, (123I/125I)IMPY, 6-iodo-2-(4'-dimethylamino-)phenyl-imidazo(1,2-a)pyridine, was successfully prepared with an iododestannylation reaction catalyzed by hydrogen peroxide. The modified **thioflavin-T** derivative displayed a good binding affinity for preformed **synthetic** Abeta40 **aggregates** in solution (Ki=15+-5 **nM**) and showed selective plaque labeling on postmortem AD brain sections. Biodistribution study in normal mice after an iv injection of (125I)IMPY exhibited excellent brain uptake (2.9% initial dose/brain at 2 min) and fast washout (0.2% initial dose/brain at 60 min). These properties are highly desirable for amyloid plaque imaging agents. In vivo plaque labeling was evaluated in a transgenic mouse model (Tg2576) engineered to produce excess amyloid plaques in the brain. Ex vivo autoradiograms of brain sections of the Tg 2576 mouse obtained at 4 h after an i.v. injection of (125I)IMPY clearly displayed a distinct plaque labeling with a low background activity. When the same brain section was stained with a fluorescent dye, thioflavin-S, the same Abeta plaques showed prominent fluorescent labeling consistent with the results of the autoradiogram. In conclusion, these findings clearly suggest that radioiodinated IMPY demonstrates desirable characteristics for in vivo labeling of Abeta plaques and it may be useful as a molecular imaging agent to study amyloidogenesis in the brain of living AD patients.
CC Behavioral biology - Human behavior 07004

oligomerization; A-beta 40 [amyloid-beta 40]; A-beta 42 [amyloid-beta 42]; DTPA; F12: medium; amyloid beta-derived diffusible ligand [ADDL]; clioquinol: chelating agent; copper; iron; zinc

IT Miscellaneous Descriptors
turbidity reading

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 67-43-6 (DTPA)
130-26-7 (clioquinol)
7440-50-8 (copper)
7439-89-6 (iron)
7440-66-6 (zinc)

L5 ANSWER 4 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:48300 BIOSIS
DN PREV200300048300
TI IMPY: An improved **thioflavin-T** derivative for in vivo labeling of beta-amyloid plaques.
AU Kung, Mei-Ping [Reprint Author]; Hou, Catherine; Zhuang, Zhi-Ping; Zhang, Bin; Skovronsky, Daniel; Trojanowski, John Q.; Lee, Virginia M.-Y.; Kung, Hank F.
CS Department of Radiology, University of Pennsylvania, 3700 Market Street, Room 305, Philadelphia, PA, 19104, USA
kungmp@sunmac.spect.upenn.edu
SO Brain Research, (29 November 2002) Vol. 956, No. 2, pp. 202-210. print.
ISSN: 0006-8993 (ISSN print).
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB Development of small molecular probes for in vivo labeling and detection of beta-amyloid (Abeta) plaques in patients of Alzheimer's disease (AD) is of significant scientific interest, and it may also assist the development of drugs targeting Abeta plaques for treatment of AD. A novel probe, (123I/125I)IMPY, 6-iodo-2-(4'-dimethylamino-)phenyl-imidazo(1,2-a)pyridine, was successfully prepared with an iododestannylation reaction catalyzed by hydrogen peroxide. The modified **thioflavin-T** derivative displayed a good binding affinity for preformed **synthetic** Abeta40 **aggregates** in solution (Ki=15+-5 **nM**) and showed selective plaque labeling on postmortem AD brain sections. Biodistribution study in normal mice after an iv injection of (125I)IMPY exhibited excellent brain uptake (2.9% initial dose/brain at 2 min) and fast washout (0.2% initial dose/brain at 60 min). These properties are highly desirable for amyloid plaque imaging agents. In vivo plaque labeling was evaluated in a transgenic mouse model (Tg2576) engineered to produce excess amyloid plaques in the brain. Ex vivo autoradiograms of brain sections of the Tg 2576 mouse obtained at 4 h after an i.v. injection of (125I)IMPY clearly displayed a distinct plaque labeling with a low background activity. When the same brain section was stained with a fluorescent dye, thioflavin-S, the same Abeta plaques showed prominent fluorescent labeling consistent with the results of the autoradiogram. In conclusion, these findings clearly suggest that radioiodinated IMPY demonstrates desirable characteristics for in vivo labeling of Abeta plaques and it may be useful as a molecular imaging agent to study amyloidogenesis in the brain of living AD patients.
CC Behavioral biology - Human behavior 07004

Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
IT Major Concepts
Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
beta-amyloid plaque: nervous system; brain: nervous system
IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)
IT Chemicals & Biochemicals
IMPY: molecular probe; beta-amyloid; hydrogen peroxide; **thioflavin-T**
IT Methods & Equipment
in vivo labeling: laboratory techniques
IT Miscellaneous Descriptors
amyloidogenesis
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model, transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 7722-84-1 (hydrogen peroxide)
2390-54-7 (**thioflavin-T**)

L5 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:43126 BIOSIS
DN PREV200300043126
TI Amyloid fibril formation by a **synthetic** peptide from a region of human acetylcholinesterase that is homologous to the Alzheimer's amyloid-beta peptide.
AU Cottingham, Matthew G.; Hollinshead, Michael S.; Vaux, David J. T. [Reprint Author]
CS Sir William Dunn School of Pathology, University of Oxford, Oxford, OX1 3RE, UK
vaux@molbiol.ox.ac.uk
SO Biochemistry, (November 19 2002) Vol. 41, No. 46, pp. 13539-13547. print. ISSN: 0006-2960 (ISSN print).
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB A region near the C-terminus of human acetylcholinesterase (AChE) is weakly homologous with the N-terminus of the Alzheimer's disease amyloid-beta peptide. We report that a 14-amino acid **synthetic** polypeptide whose sequence corresponds to residues 586-599 of the human **synaptic** or T form of AChE assembles into amyloid fibrils under physiological conditions. The fibrils have all the classical

Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
IT Major Concepts
Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
beta-amyloid plaque: nervous system; brain: nervous system
IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)
IT Chemicals & Biochemicals
IMPY: molecular probe; beta-amyloid; hydrogen peroxide; **thioflavin-T**
IT Methods & Equipment
in vivo labeling: laboratory techniques
IT Miscellaneous Descriptors
amyloidogenesis
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model, transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 7722-84-1 (hydrogen peroxide)
2390-54-7 (**thioflavin-T**)

L5 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:43126 BIOSIS
DN PREV200300043126
TI Amyloid fibril formation by a **synthetic** peptide from a region of human acetylcholinesterase that is homologous to the Alzheimer's amyloid-beta peptide.
AU Cottingham, Matthew G.; Hollinshead, Michael S.; Vaux, David J. T. [Reprint Author]
CS Sir William Dunn School of Pathology, University of Oxford, Oxford, OX1 3RE, UK
vaux@molbiol.ox.ac.uk
SO Biochemistry, (November 19 2002) Vol. 41, No. 46, pp. 13539-13547. print. ISSN: 0006-2960 (ISSN print).
DT Article
LA English
ED Entered STN: 15 Jan 2003
Last Updated on STN: 15 Jan 2003
AB A region near the C-terminus of human acetylcholinesterase (AChE) is weakly homologous with the N-terminus of the Alzheimer's disease amyloid-beta peptide. We report that a 14-amino acid **synthetic** polypeptide whose sequence corresponds to residues 586-599 of the human **synaptic** or T form of AChE assembles into amyloid fibrils under physiological conditions. The fibrils have all the classical

characteristics of amyloid: they have a diameter of 6-7 **nm** and bind both Congo red and **thioflavin-T**. Furthermore, the kinetics of assembly indicate that fibril formation proceeds via a two-step nucleation-dependent polymerization pathway, and a transition in the peptide conformation from random coil to beta-sheet is observed during fibril formation using far-UV circular dichroism spectroscopy. We also show that the peptide in **aggregated** fibrillar form has a toxic effect upon PC-12 cells in vitro. AChE normally resides mainly on cholinergic neuronal membranes, but is abnormally localized to senile plaques in Alzheimer's disease. Recently, an in vitro interaction between AChE and Abeta, the principal constituent of the amyloid fibrils in senile plaques, has been documented. The presence of a fibrillogenic region within AChE may be relevant to the interaction of AChE with amyloid fibrils formed by Abeta.

CC Behavioral biology - Human behavior 07004
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Toxicology - General and methods 22501

IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Chemicals & Biochemicals
acetylcholinesterase [EC 3.1.1.7]: activities, functions, human, molecular analysis; amyloid fibrils: analysis, formation; amyloid-beta peptide; enzymes; peptides; proteins; **synthetic** peptides

IT Methods & Equipment
far-UV circular dichroism spectroscopy: laboratory techniques, spectrum analysis techniques

IT Miscellaneous Descriptors
comparative biochemistry; molecular interactions; neuropathology; physiological conditions; toxicity

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PC-12 cell line (cell line)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 9000-81-1 (acetylcholinesterase)
9000-81-1 (EC 3.1.1.7)

L5 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1997:314054 BIOSIS
DN PREV199799604542
TI Stopped-flow kinetics reveal multiple phases of **thioflavin**

characteristics of amyloid: they have a diameter of 6-7 **nm** and bind both Congo red and **thioflavin-T**. Furthermore, the kinetics of assembly indicate that fibril formation proceeds via a two-step nucleation-dependent polymerization pathway, and a transition in the peptide conformation from random coil to beta-sheet is observed during fibril formation using far-UV circular dichroism spectroscopy. We also show that the peptide in **aggregated** fibrillar form has a toxic effect upon PC-12 cells in vitro. AChE normally resides mainly on cholinergic neuronal membranes, but is abnormally localized to senile plaques in Alzheimer's disease. Recently, an in vitro interaction between AChE and Abeta, the principal constituent of the amyloid fibrils in senile plaques, has been documented. The presence of a fibrillogenic region within AChE may be relevant to the interaction of AChE with amyloid fibrils formed by Abeta.

CC Behavioral biology - Human behavior 07004
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Toxicology - General and methods 22501

IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)

IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)

IT Chemicals & Biochemicals
acetylcholinesterase [EC 3.1.1.7]: activities, functions, human, molecular analysis; amyloid fibrils: analysis, formation; amyloid-beta peptide; enzymes; peptides; proteins; **synthetic** peptides

IT Methods & Equipment
far-UV circular dichroism spectroscopy: laboratory techniques, spectrum analysis techniques

IT Miscellaneous Descriptors
comparative biochemistry; molecular interactions; neuropathology; physiological conditions; toxicity

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PC-12 cell line (cell line)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 9000-81-1 (acetylcholinesterase)
9000-81-1 (EC 3.1.1.7)

L5 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1997:314054 BIOSIS
DN PREV199799604542
TI Stopped-flow kinetics reveal multiple phases of **thioflavin**

**T** binding to Alzheimer beta(1-40) amyloid fibrils.
AU Levine, Harry Iii
CS Neurodegenerative Diseases, Parke-Davis Pharmaceutical Research Div., Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, MI 48105-1047, USA
SO Archives of Biochemistry and Biophysics, (1997) Vol. 342, No. 2, pp. 306-316.
CODEN: ABBIA4. ISSN: 0003-9861.
DT Article
LA English
ED Entered STN: 26 Jul 1997
Last Updated on STN: 4 Sep 1997
AB The benzothiazole dye **thioflavin T** (ThT) is a classical amyloid stain for senile plaques containing beta/A4 peptide in Alzheimer's disease brain. ThT also binds rapidly and specifically to the anti-parallel beta-sheet fibrils formed from **synthetic** beta(1-40) peptide, but does not bind to monomer or oligomeric intermediates. The fibrillar beta-sheet-bound dye species undergoes a characteristic 120 **nm** red shift of its excitation spectrum that may be selectively excited at 450 **nm**, resulting in a fluorescence signal at 482 **nm**. Mixing of preformed beta(1-40) amyloid fibrils with ThT in a stopped-flow spectrophotometer, monitoring fluorescence emission at gt 475 **nm** while exciting at 450 **nm**, distinguished multiple kinetic phases of roughly equivalent amplitude with tau's in the ranges of 0.007, 0.05, 0.75, and 10-20 s. The fastest reaction appears to reflect a bimolecular dye binding event while the remaining reactions are rate-limited by protein tertiary or quaternary conformational changes. The high activation energies of the three slower reactions support this interpretation. The ThT concentration dependence of the reaction rates at different ratios of ThT/beta(1-40) amyloid fibrils rules out a rate-limiting conformational change occurring prior to ligand binding. ThT is a useful probe for the **aggregated** fibrillar state of beta(1-40) amyloid fibrils as the amyloid-specific fluorescence reports only fibrillar species. The binding of ThT does not interfere with the **aggregation** of this peptide into amyloid fibrils. The putative conformational changes detected by the ThT fluorescence suggest that small pharmacologic ligands can perturb and possibly dissociate A-beta amyloid fibrils.
CC Biochemistry studies - General 10060
Biophysics - General 10502
Nervous system - General and methods 20501
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
THIOFLAVIN; AMYLOID
IT Time
Quaternary; Tertiary
IT Miscellaneous Descriptors
ACTIVATION ENERGY; ALZHEIMER BETA(1-40) AMYLOID FIBRILS; ALZHEIMER'S DISEASE; BEHAVIORAL AND MENTAL DISORDERS; BIOCHEMISTRY AND BIOPHYSICS; BRAIN; CONFORMATIONAL CHANGES; KINETIC PHASES; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; PHARMACOLOGIC LIGANDS; RATE-LIMITING; STOPPED-FLOW KINETICS; **THIOFLAVIN T** BINDING
RN 2390-54-7 (THIOFLAVIN)
11061-24-8 (AMYLOID)

L5 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:327565 CAPLUS
ED Entered STN: 18 Apr 2005
TI Neurotoxic effect of rotenone on dopaminergic neurons
AU Qi, Chen; Liu, Zhenguo; Fan, Guohua; Chen, Shengdi; Lu, Guoqiang
CS Ruijin Hospital, Shanghai Second Medical University, Shanghai, 200025, Peop. Rep. China

**T** binding to Alzheimer beta(1-40) amyloid fibrils.
AU Levine, Harry Iii
CS Neurodegenerative Diseases, Parke-Davis Pharmaceutical Research Div., Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, MI 48105-1047, USA
SO Archives of Biochemistry and Biophysics, (1997) Vol. 342, No. 2, pp. 306-316.
CODEN: ABBIA4. ISSN: 0003-9861.
DT Article
LA English
ED Entered STN: 26 Jul 1997
Last Updated on STN: 4 Sep 1997
AB The benzothiazole dye **thioflavin T** (ThT) is a classical amyloid stain for senile plaques containing beta/A4 peptide in Alzheimer's disease brain. ThT also binds rapidly and specifically to the anti-parallel beta-sheet fibrils formed from **synthetic** beta(1-40) peptide, but does not bind to monomer or oligomeric intermediates. The fibrillar beta-sheet-bound dye species undergoes a characteristic 120 **nm** red shift of its excitation spectrum that may be selectively excited at 450 **nm**, resulting in a fluorescence signal at 482 **nm**. Mixing of preformed beta(1-40) amyloid fibrils with ThT in a stopped-flow spectrophotometer, monitoring fluorescence emission at gt 475 **nm** while exciting at 450 **nm**, distinguished multiple kinetic phases of roughly equivalent amplitude with tau's in the ranges of 0.007, 0.05, 0.75, and 10-20 s. The fastest reaction appears to reflect a bimolecular dye binding event while the remaining reactions are rate-limited by protein tertiary or quaternary conformational changes. The high activation energies of the three slower reactions support this interpretation. The ThT concentration dependence of the reaction rates at different ratios of ThT/beta(1-40) amyloid fibrils rules out a rate-limiting conformational change occurring prior to ligand binding. ThT is a useful probe for the **aggregated** fibrillar state of beta(1-40) amyloid fibrils as the amyloid-specific fluorescence reports only fibrillar species. The binding of ThT does not interfere with the **aggregation** of this peptide into amyloid fibrils. The putative conformational changes detected by the ThT fluorescence suggest that small pharmacologic ligands can perturb and possibly dissociate A-beta amyloid fibrils.
CC Biochemistry studies - General 10060
Biophysics - General 10502
Nervous system - General and methods 20501
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
THIOFLAVIN; AMYLOID
IT Time
Quaternary; Tertiary
IT Miscellaneous Descriptors
ACTIVATION ENERGY; ALZHEIMER BETA(1-40) AMYLOID FIBRILS; ALZHEIMER'S DISEASE; BEHAVIORAL AND MENTAL DISORDERS; BIOCHEMISTRY AND BIOPHYSICS; BRAIN; CONFORMATIONAL CHANGES; KINETIC PHASES; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; PHARMACOLOGIC LIGANDS; RATE-LIMITING; STOPPED-FLOW KINETICS; **THIOFLAVIN T** BINDING
RN 2390-54-7 (THIOFLAVIN)
11061-24-8 (AMYLOID)

L5 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:327565 CAPLUS
ED Entered STN: 18 Apr 2005
TI Neurotoxic effect of rotenone on dopaminergic neurons
AU Qi, Chen; Liu, Zhenguo; Fan, Guohua; Chen, Shengdi; Lu, Guoqiang
CS Ruijin Hospital, Shanghai Second Medical University, Shanghai, 200025, Peop. Rep. China

SO Zhonghua Shenjingke Zazhi (2004), 37(6), 538-542
CODEN: ZSZAFN; ISSN: 1006-7876
PB Zhonghua Yixuehui Zazhishe
DT Journal
LA Chinese
CC 4 (Toxicology)
AB The mechanism of rotenone neurotoxicity on dopaminergic neurons was investigated. PC12 cells differentiated by nerve growth factor as dopaminergic neurons were treated by different concns. of rotenone. Cell viability was assessed with MTT, and cell apoptosis was detected by Annexin-V staining and flow cytometry. The double staining with α-**synuclein** and **thioflavin T** was used to observe protein **aggregation**. After being treated with rotenone for 24 h, the process-like structures of PC12 cells disappeared, and the cell body became smaller and smoother in time- and concentration-dependent manners. Compared with the control group, the cell viability began to decline significantly when treated by rotenone at concentration of 10 **nmol**/L (A570 0.415±0.013) ($P<0.05$). The early sign of apoptosis was found with Annexin-V pos. staining. The apoptotic rate was 7.35%±0.52% at rotenone concentration of 5 **nmol**/L ($P<0.05$), and was 13.30%±1.80% at concentration of 10 **nmol**/L ($P<0.01$). Protein **aggregation** with the double pos. staining of α- **synuclein** and **thioflavin T** were also found in the groups treated by rotenone. In vitro, rotenone should be neurotoxic to dopaminergic neurons, inducing apoptosis and inclusion of α- **synuclein** **aggregation**. Rotenone might act through the metabolism of α-**synuclein** in the pathogenesis of Parkinson's disease.
ST rotenone neurotoxicity dopaminergic neuron Parkinson disease

L5 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:827673 CAPLUS
DN 137:59572
ED Entered STN: 14 Nov 2001
TI IBOX (2-(4'-dimethylaminophenyl)-6-iodobenzoxazole): a ligand for imaging amyloid plaques in the brain
AU Zhuang, Zhi-Ping; Kung, Mei-Ping; Hou, Catherine; Plossl, Karl; Skovronsky, Daniel; Gur, Tamar L.; Trojanowski, John Q.; Lee, Virginia M.-Y.; Kung, Hank F.
CS Department of Radiology, University of Pennsylvania, Philadelphia, PA, 19104, USA
SO Nuclear Medicine and Biology (2001), 28(8), 887-894
CODEN: NMBIEO; ISSN: 0969-8051
PB Elsevier Science Inc.
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
Section cross-reference(s): 28
AB It is well known that overprodn. and accumulation of β-amyloid (Aβ) plaques in the brain is a key event in the pathogenesis of Alzheimer's disease (AD). Previously it was demonstrated that [125I]TZDM, 2-(4'-dimethylaminophenyl)-6-iodobenzothiazole, a thioflavin derivative, was an effective ligand with good in vitro and in vivo binding characteristics. To further improve the initial uptake and washout rate from the brain, important properties for in vivo imaging agents, a novel radioiodinated ligand, 2-(4'-dimethylaminophenyl)-6-iodobenzoxazole ([125I]IBOX), for detecting Aβ plaques in the brain, was **synthesized** and evaluated. The new iodinated ligand, IBOX, is based on an isosteric replacement of a sulfur atom of TZDM by an oxygen, by which the mol. weight is reduced while the lipophilicity of the iodinated ligand is increased. Partition coeffs. (P.C.) of these two ligands were 70 and 124 for TZDM and IBOX, resp. In vitro binding study indicated that the isosteric displacement yielded a new ligand with equal binding potency to Aβ(1-40) **aggregates** (Ki = 1.9 and 0.8 **nM** for

SO Zhonghua Shenjingke Zazhi (2004), 37(6), 538-542
CODEN: ZSZAFN; ISSN: 1006-7876
PB Zhonghua Yixuehui Zazhishe
DT Journal
LA Chinese
CC 4 (Toxicology)
AB The mechanism of rotenone neurotoxicity on dopaminergic neurons was investigated. PC12 cells differentiated by nerve growth factor as dopaminergic neurons were treated by different concns. of rotenone. Cell viability was assessed with MTT, and cell apoptosis was detected by Annexin-V staining and flow cytometry. The double staining with α-**synuclein** and **thioflavin T** was used to observe protein **aggregation**. After being treated with rotenone for 24 h, the process-like structures of PC12 cells disappeared, and the cell body became smaller and smoother in time- and concentration-dependent manners. Compared with the control group, the cell viability began to decline significantly when treated by rotenone at concentration of 10 **nmol**/L (A570 0.415±0.013) ($P<0.05$). The early sign of apoptosis was found with Annexin-V pos. staining. The apoptotic rate was 7.35%±0.52% at rotenone concentration of 5 **nmol**/L ($P<0.05$), and was 13.30%±1.80% at concentration of 10 **nmol**/L ($P<0.01$). Protein **aggregation** with the double pos. staining of α- **synuclein** and **thioflavin T** were also found in the groups treated by rotenone. In vitro, rotenone should be neurotoxic to dopaminergic neurons, inducing apoptosis and inclusion of α- **synuclein** **aggregation**. Rotenone might act through the metabolism of α-**synuclein** in the pathogenesis of Parkinson's disease.
ST rotenone neurotoxicity dopaminergic neuron Parkinson disease

L5 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:827673 CAPLUS
DN 137:59572
ED Entered STN: 14 Nov 2001
TI IBOX (2-(4'-dimethylaminophenyl)-6-iodobenzoxazole): a ligand for imaging amyloid plaques in the brain
AU Zhuang, Zhi-Ping; Kung, Mei-Ping; Hou, Catherine; Plossl, Karl; Skovronsky, Daniel; Gur, Tamar L.; Trojanowski, John Q.; Lee, Virginia M.-Y.; Kung, Hank F.
CS Department of Radiology, University of Pennsylvania, Philadelphia, PA, 19104, USA
SO Nuclear Medicine and Biology (2001), 28(8), 887-894
CODEN: NMBIEO; ISSN: 0969-8051
PB Elsevier Science Inc.
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
Section cross-reference(s): 28
AB It is well known that overprodn. and accumulation of β-amyloid (Aβ) plaques in the brain is a key event in the pathogenesis of Alzheimer's disease (AD). Previously it was demonstrated that [125I]TZDM, 2-(4'-dimethylaminophenyl)-6-iodobenzothiazole, a thioflavin derivative, was an effective ligand with good in vitro and in vivo binding characteristics. To further improve the initial uptake and washout rate from the brain, important properties for in vivo imaging agents, a novel radioiodinated ligand, 2-(4'-dimethylaminophenyl)-6-iodobenzoxazole ([125I]IBOX), for detecting Aβ plaques in the brain, was **synthesized** and evaluated. The new iodinated ligand, IBOX, is based on an isosteric replacement of a sulfur atom of TZDM by an oxygen, by which the mol. weight is reduced while the lipophilicity of the iodinated ligand is increased. Partition coeffs. (P.C.) of these two ligands were 70 and 124 for TZDM and IBOX, resp. In vitro binding study indicated that the isosteric displacement yielded a new ligand with equal binding potency to Aβ(1-40) **aggregates** (Ki = 1.9 and 0.8 **nM** for

TZDM and IBOX, resp.). Autoradiog. of postmortem brain sections of a confirmed AD patient by [125I]IBOX showed excellent labeling of plaques similar to that observed with [125I]TZDM. More importantly, in vivo biodistribution of [125I]IBOX in normal mice displayed superior peak brain uptake (2.08% at 30 min vs 1.57% at 60 min dose/brain for [125I]IBOX and [125I]TZDM, resp.). In addition, the washout from the brain was much faster for [125I]IBOX as compared to [125I]TZDM. Based on the data presented for [125I]IBOX, it is predicted that the brain trapping of this new radioiodinated ligand in the Aβ containing regions will be more favorable than that of the parent compound, [125I]TZDM. Further evaluation of [125I]IBOX is warranted to confirm the Aβ plaque labeling properties in vivo.

ST brain amyloid plaque imaging iodine 125 benzoxazole prepn; Alzheimer brain SPECT radioiodinated ligand prepn

IT Radiography
(autoradiography; radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT Alzheimer's disease
Brain
Human
Single-photon-emission computed tomography
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT Amyloid
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-; radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 439586-36-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 439586-38-6P
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 121-88-0, 5-Nitro-2-aminophenol 619-84-1, 4-Dimethylaminobenzoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 118040-54-3P 439586-35-3P 439586-37-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 346691-96-1
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); BIOL (Biological study); USES (Uses)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain: comparison with [125I]TZDM)

IT 2390-54-7, **Thioflavin T** 346691-79-0 346691-94-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain: effect of thioflavins on [125I]TZDM binding)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Agdeppa, E; J Lab Compds Radiopharm 2001, V44, PS242
(2) Agdeppa, E; J Nucl Med 2001, V42, P65P
(3) Agdeppa, E; J Nucl Med 2001, V42, PS64P
(4) Ashburn, T; Chem Biol 1996, V3, P351 CAPLUS
(5) Dezutter, N; Eur J Nucl Med 1999, V26, P1392 CAPLUS
(6) Dezutter, N; J Lab Compds Radiopharm 1999, V42, P309 CAPLUS

TZDM and IBOX, resp.). Autoradiog. of postmortem brain sections of a confirmed AD patient by [125I]IBOX showed excellent labeling of plaques similar to that observed with [125I]TZDM. More importantly, in vivo biodistribution of [125I]IBOX in normal mice displayed superior peak brain uptake (2.08% at 30 min vs 1.57% at 60 min dose/brain for [125I]IBOX and [125I]TZDM, resp.). In addition, the washout from the brain was much faster for [125I]IBOX as compared to [125I]TZDM. Based on the data presented for [125I]IBOX, it is predicted that the brain trapping of this new radioiodinated ligand in the Aβ containing regions will be more favorable than that of the parent compound, [125I]TZDM. Further evaluation of [125I]IBOX is warranted to confirm the Aβ plaque labeling properties in vivo.

ST brain amyloid plaque imaging iodine 125 benzoxazole prepn; Alzheimer brain SPECT radioiodinated ligand prepn

IT Radiography
(autoradiography; radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT Alzheimer's disease
Brain
Human
Single-photon-emission computed tomography
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT Amyloid
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-; radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 439586-36-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 439586-38-6P
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 121-88-0, 5-Nitro-2-aminophenol 619-84-1, 4-Dimethylaminobenzoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 118040-54-3P 439586-35-3P 439586-37-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain)

IT 346691-96-1
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); BIOL (Biological study); USES (Uses)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain: comparison with [125I]TZDM)

IT 2390-54-7, **Thioflavin T** 346691-79-0 346691-94-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(radioiodinated (dimethylaminophenyl)iodobenzoxazole for imaging amyloid plaques in brain: effect of thioflavins on [125I]TZDM binding)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Agdeppa, E; J Lab Compds Radiopharm 2001, V44, PS242
(2) Agdeppa, E; J Nucl Med 2001, V42, P65P
(3) Agdeppa, E; J Nucl Med 2001, V42, PS64P
(4) Ashburn, T; Chem Biol 1996, V3, P351 CAPLUS
(5) Dezutter, N; Eur J Nucl Med 1999, V26, P1392 CAPLUS
(6) Dezutter, N; J Lab Compds Radiopharm 1999, V42, P309 CAPLUS

(7) Elhaddaoui, A; Biospectroscopy 1995, V1, P351 CAPLUS
(8) Ginsberg, S; Cerebral cortex: neurodegenerative and agerelated changes in structure and function of cerebral cortex 1999, P603 CAPLUS
(9) Golde, T; Biochem Biophys Acta 2000, V1502, P172 CAPLUS
(10) Han, G; J Am Chem Soc 1996, V118, P4506
(11) Klunk, W; Biol Psychiatry 1994, V35, P627
(12) Klunk, W; Life Sci 1998, V63, P1807 CAPLUS
(13) Klunk, W; Neurobiol Aging 1995, V16, P541 MEDLINE
(14) Klunk, W; Society for Neuroscience Abstracts 1997, V23, P1638
(15) Lee, V; Neuron 1999, V24, P507 CAPLUS
(16) Link, C; Neurobiol Aging 2001, V22, P217 CAPLUS
(17) Lippa, C; Neurology 2000, V54, P100 MEDLINE
(18) Lorenzo, A; Proc Natl Acad Sci USA 1994, V91, P12243 CAPLUS
(19) Mathis, C; J Lab Compds Radiopharm 1997, V39, PS94
(20) Mathis, C; J Lab Compds Radiopharm 2001, V44, PS26
(21) Mathis, C; J Nucl Med 2001, V42, P113P
(22) Mathis, C; J Nucl Med 2001, V42, P252P
(23) Munson, P; Anal Biochem 1980, V107, P220 CAPLUS
(24) Selkoe, D; Alzheimer's Disease 1999, P293
(25) Selkoe, D; JAMA 2000, V283, P1615 MEDLINE
(26) Selkoe, D; Science 1997, V275, P630 CAPLUS
(27) Skovronsky, D; Proc Natl Acad Sci USA 2000, V97, P7609 CAPLUS
(28) Styren, S; J Histochem Cytochem 2000, V48, P1223 CAPLUS
(29) Terashima, M; Synthesis 1982, V484-5
(30) Zhen, W; J Med Chem 1999, V42, P2805 CAPLUS
(31) Zhuang, Z; J Med Chem 2001, V44, P1905 CAPLUS

L5 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:444464 CAPLUS
DN 119:44464
ED Entered STN: 07 Aug 1993
TI **Thioflavin T** interaction with **synthetic** Alzheimer's disease β-amyloid peptides: Detection of amyloid **aggregation** in solution
AU LeVine, Harry, III
CS Dep. Neurosci. Pharmacol., Warner-Lambert Co., Ann Arbor, MI, 48106-1047, USA
SO Protein Science (1993), 2(3), 404-10
CODEN: PRCIEI; ISSN: 0961-8368
DT Journal
LA English
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 14
AB Thioflavine T (ThT) assocs. rapidly with **aggregated** fibrils of the **synthetic** β/A4-derived peptides β(1-28) and β(1-40), giving rise to a new excitation (ex) (absorption) maximum at 450 **nm** and enhanced emission (em) at 482 **nm**, as opposed to the 385 **nm** (ex) and 445 **nm** (em) of the free dye. This change is dependent on the **aggregated** state as monomeric or dimeric peptides do not react, and guanidine dissociation of **aggregates** destroys the signal. There was no effect of high salt concns. Binding to the β(1-40) is of lower affinity, Kd 2 μM, while it sats. with a Kd of 0.54 μM for β(1-28). Insulin fibrils converted to a β-sheet conformation fluoresce intensely with ThT. A variety of polyhydroxy, polyanionic, or polycationic materials fail to interact or impede interaction with the amyloid peptides. This fluorometric technique should allow the kinetic elucidation of the amyloid fibril assembly process as well as the testing of agents that might modulate their assembly or disassembly.
ST thioflavine T amyloid protein fluorescence Alzheimer
IT Mental disorder
(Alzheimer's disease, pathogenesis of, amyloid fibril formation in, thioflavine T interaction with **synthetic** β-amyloid

(7) Elhaddaoui, A; Biospectroscopy 1995, V1, P351 CAPLUS
(8) Ginsberg, S; Cerebral cortex: neurodegenerative and agerelated changes in structure and function of cerebral cortex 1999, P603 CAPLUS
(9) Golde, T; Biochem Biophys Acta 2000, V1502, P172 CAPLUS
(10) Han, G; J Am Chem Soc 1996, V118, P4506
(11) Klunk, W; Biol Psychiatry 1994, V35, P627
(12) Klunk, W; Life Sci 1998, V63, P1807 CAPLUS
(13) Klunk, W; Neurobiol Aging 1995, V16, P541 MEDLINE
(14) Klunk, W; Society for Neuroscience Abstracts 1997, V23, P1638
(15) Lee, V; Neuron 1999, V24, P507 CAPLUS
(16) Link, C; Neurobiol Aging 2001, V22, P217 CAPLUS
(17) Lippa, C; Neurology 2000, V54, P100 MEDLINE
(18) Lorenzo, A; Proc Natl Acad Sci USA 1994, V91, P12243 CAPLUS
(19) Mathis, C; J Lab Compds Radiopharm 1997, V39, PS94
(20) Mathis, C; J Lab Compds Radiopharm 2001, V44, PS26
(21) Mathis, C; J Nucl Med 2001, V42, P113P
(22) Mathis, C; J Nucl Med 2001, V42, P252P
(23) Munson, P; Anal Biochem 1980, V107, P220 CAPLUS
(24) Selkoe, D; Alzheimer's Disease 1999, P293
(25) Selkoe, D; JAMA 2000, V283, P1615 MEDLINE
(26) Selkoe, D; Science 1997, V275, P630 CAPLUS
(27) Skovronsky, D; Proc Natl Acad Sci USA 2000, V97, P7609 CAPLUS
(28) Styren, S; J Histochem Cytochem 2000, V48, P1223 CAPLUS
(29) Terashima, M; Synthesis 1982, V484-5
(30) Zhen, W; J Med Chem 1999, V42, P2805 CAPLUS
(31) Zhuang, Z; J Med Chem 2001, V44, P1905 CAPLUS

L5 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:444464 CAPLUS
DN 119:44464
ED Entered STN: 07 Aug 1993
TI **Thioflavin T** interaction with **synthetic** Alzheimer's disease β-amyloid peptides: Detection of amyloid **aggregation** in solution
AU LeVine, Harry, III
CS Dep. Neurosci. Pharmacol., Warner-Lambert Co., Ann Arbor, MI, 48106-1047, USA
SO Protein Science (1993), 2(3), 404-10
CODEN: PRCIEI; ISSN: 0961-8368
DT Journal
LA English
CC 9-5 (Biochemical Methods)
Section cross-reference(s): 14
AB Thioflavine T (ThT) assocs. rapidly with **aggregated** fibrils of the **synthetic** β/A4-derived peptides β(1-28) and β(1-40), giving rise to a new excitation (ex) (absorption) maximum at 450 **nm** and enhanced emission (em) at 482 **nm**, as opposed to the 385 **nm** (ex) and 445 **nm** (em) of the free dye. This change is dependent on the **aggregated** state as monomeric or dimeric peptides do not react, and guanidine dissociation of **aggregates** destroys the signal. There was no effect of high salt concns. Binding to the β(1-40) is of lower affinity, Kd 2 μM, while it sats. with a Kd of 0.54 μM for β(1-28). Insulin fibrils converted to a β-sheet conformation fluoresce intensely with ThT. A variety of polyhydroxy, polyanionic, or polycationic materials fail to interact or impede interaction with the amyloid peptides. This fluorometric technique should allow the kinetic elucidation of the amyloid fibril assembly process as well as the testing of agents that might modulate their assembly or disassembly.
ST thioflavine T amyloid protein fluorescence Alzheimer
IT Mental disorder
(Alzheimer's disease, pathogenesis of, amyloid fibril formation in, thioflavine T interaction with **synthetic** β-amyloid

protein-derived peptide fragments studied by fluorometry in relation to)

IT Proteins, specific or class
RL: ANST (Analytical study)
(amyloid A4, **synthetic** peptides derived from, thioflavine T interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)

IT 2390-54-7, Thioflavine T
RL: ANST (Analytical study)
(**synthetic** β-amyloid peptide interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)

L5 ANSWER 10 OF 12 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 86011167 EMBASE
DN 1986011167
TI Immunotactoid glomerulopathy.
AU Korbert S.M.; Schwartz M.M.; Rosenberg B.F.; et al.
CS Section of Nephrology, Department of Medicine and Pathology, Rush Medical College, Chicago, IL, United States
SO Medicine, (1985) Vol. 64, No. 4, pp. 228-243.
CODEN: MEDIAV
CY United States
DT Journal
FS 006 Internal Medicine
028 Urology and Nephrology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
ED Entered STN: 911210
Last Updated on STN: 911210
AB We present 11 patients with immunotactoid glomerulopathy, a new **syndrome** characterized clinically by proteinuria (11/11), microscopic hematuria (9/11) and hypertension (9/11). The patients consisted of six females and five males, aged 25 to 59 years (mean, 44.6). Proteinuria was the presenting feature and the reason for renal biopsy in all patients. The diagnosis of immunotactoid glomerulopathy was established at renal biopsy by the presence of glomerular extracellular microtubules composed of immune reactants. All the biopsies studied by immunofluorescence (10 cases) had glomerular deposits of IgG and C3. In three biopsies studied with IgG subclass specific antisera, only one patient had monoclonal immunoglobulin deposits (IgG3 kappa). In six cases the glomerular deposits were analyzed for light chains. In three the deposits contained kappa only, and three consisted of both kappa and lambda. In two cases the immune **aggregates** were confined to the mesangium, and in the remaining eight cases, the deposits were present in the mesangium and the glomerular basement membranes. Electron-dense deposits composed of microtubules were present in the same distribution within the glomerulus as the immune reactants. The microtubules had a uniform diameter in each biopsy, but they varied in size from case to case. They were approximately the same size in eight cases (mean, 22.3 ± 3 [SD] **nm**). Three cases had much larger microtubules: 34.2 **nm**, 35.4 **nm**, and 48.9 **nm** in diameter.
Although the 22.3-**nm** microtubules resembled amyloid in their appearance, glomerular distribution and random orientation in the tissue, they were more than twice the diameter of amyloid (8.9 **nm**), and Congo red and **thioflavin T** stains for amyloid were negative. Similar microtubular structures have been described in patients with cryoglobulinemia, SLE and paraproteinemia, but these diseases were excluded in our patients on clinical, serologic and in some case histologic grounds. More important, none of our patients had clinical or histochemical evidence of amyloidosis, an entity which may be confused

protein-derived peptide fragments studied by fluorometry in relation to)

IT Proteins, specific or class
RL: ANST (Analytical study)
(amyloid A4, **synthetic** peptides derived from, thioflavine T interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)

IT 2390-54-7, Thioflavine T
RL: ANST (Analytical study)
(**synthetic** β-amyloid peptide interaction with, fluorometry in study of, Alzheimer's disease pathogenesis and amyloid fibril formation in relation to)

L5 ANSWER 10 OF 12 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 86011167 EMBASE
DN 1986011167
TI Immunotactoid glomerulopathy.
AU Korbert S.M.; Schwartz M.M.; Rosenberg B.F.; et al.
CS Section of Nephrology, Department of Medicine and Pathology, Rush Medical College, Chicago, IL, United States
SO Medicine, (1985) Vol. 64, No. 4, pp. 228-243.
CODEN: MEDIAV
CY United States
DT Journal
FS 006 Internal Medicine
028 Urology and Nephrology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
ED Entered STN: 911210
Last Updated on STN: 911210
AB We present 11 patients with immunotactoid glomerulopathy, a new **syndrome** characterized clinically by proteinuria (11/11), microscopic hematuria (9/11) and hypertension (9/11). The patients consisted of six females and five males, aged 25 to 59 years (mean, 44.6). Proteinuria was the presenting feature and the reason for renal biopsy in all patients. The diagnosis of immunotactoid glomerulopathy was established at renal biopsy by the presence of glomerular extracellular microtubules composed of immune reactants. All the biopsies studied by immunofluorescence (10 cases) had glomerular deposits of IgG and C3. In three biopsies studied with IgG subclass specific antisera, only one patient had monoclonal immunoglobulin deposits (IgG3 kappa). In six cases the glomerular deposits were analyzed for light chains. In three the deposits contained kappa only, and three consisted of both kappa and lambda. In two cases the immune **aggregates** were confined to the mesangium, and in the remaining eight cases, the deposits were present in the mesangium and the glomerular basement membranes. Electron-dense deposits composed of microtubules were present in the same distribution within the glomerulus as the immune reactants. The microtubules had a uniform diameter in each biopsy, but they varied in size from case to case. They were approximately the same size in eight cases (mean, 22.3 ± 3 [SD] **nm**). Three cases had much larger microtubules: 34.2 **nm**, 35.4 **nm**, and 48.9 **nm** in diameter.
Although the 22.3-**nm** microtubules resembled amyloid in their appearance, glomerular distribution and random orientation in the tissue, they were more than twice the diameter of amyloid (8.9 **nm**), and Congo red and **thioflavin T** stains for amyloid were negative. Similar microtubular structures have been described in patients with cryoglobulinemia, SLE and paraproteinemia, but these diseases were excluded in our patients on clinical, serologic and in some case histologic grounds. More important, none of our patients had clinical or histochemical evidence of amyloidosis, an entity which may be confused

with immunotactoid glomerulopathy on a morphologic basis. Follow-up, from 22 to 94 months (mean, 52.6) was obtained in all 11 patients, and 2 clinical courses were noted. Six patients had progressive deterioration of renal function, with five requiring dialysis. This group had severe hypertension (4/6) and nephrotic-range proteinuria (5/6) at some point in their course. The remaining five patients with stable renal function had proteinuria of less than 2.0 g/24 hr in most cases (4/5), and none had severe hypertension. This dichotomy correlated with the distribution of immunotactoids. The patients with progressive renal insufficiency had extensive deposits involving both the mesangium and glomerular capillary walls. In contrast, the patients with less widely distributed deposits appeared to have a more stable course. Immunotactoid glomerulopathy represents a **syndrome** with characteristic morphologic and ultrastructural features. The immunotactoid microtubules are heterogeneous in size and immunoglobulin composition. Although the pathogenesis of this lesion is not known, the immunotactoids appear to represent immune reactants with a degree of ultrastructural organization which is greater than that of the various organized cryoglobulins but less than the highly structured beta-pleated sheet of amyloid. It is hoped that increased awareness of immunotactoids and further characterization of their ultrastructural composition will shed light on this newly described entity.

CT Medical Descriptors:
*glomerulonephritis
*glomerulopathy
hematuria
hypertension
kidney biopsy
proteinuria
cardiovascular system
diagnosis
kidney
priority journal
adult
etiology
clinical article
human
blood and hemopoietic system
urinary tract
Drug Descriptors:
*complement component c3
*immunoglobulin g

RN (complement component c3) 80295-41-6; (immunoglobulin g) 97794-27-9

L5 ANSWER 11 OF 12 MEDLINE on STN
AN 1998169534 MEDLINE
DN PubMed ID: 9501253
TI Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation.
AU Hughes S R; Khorkova O; Goyal S; Knaeblein J; Heroux J; Riedel N G; Sahasrabudhe S
CS Biotechnology Group and the Central Nervous System Disease Group, Hoechst Marion Roussel, Inc., P.O. Box 6800, Bridgewater, NJ 08876-0800, USA.
SO Proceedings of the National Academy of Sciences of the United States of America, (1998 Mar 17) 95 (6) 3275-80.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980422
Last Updated on STN: 19980422

with immunotactoid glomerulopathy on a morphologic basis. Follow-up, from 22 to 94 months (mean, 52.6) was obtained in all 11 patients, and 2 clinical courses were noted. Six patients had progressive deterioration of renal function, with five requiring dialysis. This group had severe hypertension (4/6) and nephrotic-range proteinuria (5/6) at some point in their course. The remaining five patients with stable renal function had proteinuria of less than 2.0 g/24 hr in most cases (4/5), and none had severe hypertension. This dichotomy correlated with the distribution of immunotactoids. The patients with progressive renal insufficiency had extensive deposits involving both the mesangium and glomerular capillary walls. In contrast, the patients with less widely distributed deposits appeared to have a more stable course. Immunotactoid glomerulopathy represents a **syndrome** with characteristic morphologic and ultrastructural features. The immunotactoid microtubules are heterogeneous in size and immunoglobulin composition. Although the pathogenesis of this lesion is not known, the immunotactoids appear to represent immune reactants with a degree of ultrastructural organization which is greater than that of the various organized cryoglobulins but less than the highly structured beta-pleated sheet of amyloid. It is hoped that increased awareness of immunotactoids and further characterization of their ultrastructural composition will shed light on this newly described entity.

CT Medical Descriptors:
*glomerulonephritis
*glomerulopathy
hematuria
hypertension
kidney biopsy
proteinuria
cardiovascular system
diagnosis
kidney
priority journal
adult
etiology
clinical article
human
blood and hemopoietic system
urinary tract
Drug Descriptors:
*complement component c3
*immunoglobulin g

RN (complement component c3) 80295-41-6; (immunoglobulin g) 97794-27-9

L5 ANSWER 11 OF 12 MEDLINE on STN
AN 1998169534 MEDLINE
DN PubMed ID: 9501253
TI Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation.
AU Hughes S R; Khorkova O; Goyal S; Knaeblein J; Heroux J; Riedel N G; Sahasrabudhe S
CS Biotechnology Group and the Central Nervous System Disease Group, Hoechst Marion Roussel, Inc., P.O. Box 6800, Bridgewater, NJ 08876-0800, USA.
SO Proceedings of the National Academy of Sciences of the United States of America, (1998 Mar 17) 95 (6) 3275-80.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980422
Last Updated on STN: 19980422

Entered Medline: 19980410

AB We have used the yeast two-hybrid system to isolate cDNAs encoding proteins that specifically interact with the 42-aa beta-amyloid peptide (Abeta), a major constituent of senile plaques in Alzheimer's disease. The carboxy terminus of alpha2-macroglobulin (alpha2M), a proteinase inhibitor released in response to inflammatory stimuli, was identified as a strong and specific interactor of Abeta, utilizing this system. Direct evidence for this interaction was obtained by co-immunoprecipitation of alpha2M with Abeta from the yeast cell, and by formation of SDS-resistant Abeta complexes in polyacrylamide gels by using **synthetic** Abeta and purified alpha2M. The association of Abeta with alpha2M and various purified amyloid binding proteins was assessed by employing a method measuring protein-protein interactions in liquid phase. The dissociation constant by this technique for the alpha2M-Abeta association using labeled purified proteins was measured (Kd = 350 **nM**). Electron microscopy showed that a 1:8 ratio of alpha2M to Abeta prevented fibril formation in solution; the same ratio to Abeta of another acute phase protein, alpha1-antichymotrypsin, was not active in preventing fibril formation in vitro. These results were corroborated by data obtained from an in vitro **aggregation** assay employing Thioflavine T. The interaction of alpha2M with Abeta suggests new pathway(s) for the clearance of the soluble amyloid peptide.

CT *Amyloid beta-Protein: ME, metabolism
Biotinylation
DNA, Complementary
Hela Cells
Humans
Neurofibrils
*Peptide Fragments: ME, metabolism
Precipitin Tests
*Protease Inhibitors: ME, metabolism
Protein Binding
Thiazoles
alpha-Macroglobulins: GE, genetics
*alpha-Macroglobulins: ME, metabolism

RN **2390-54-7 (thioflavin T)**

CN 0 (Amyloid beta-Protein); 0 (DNA, Complementary); 0 (Peptide Fragments); 0 (Protease Inhibitors); 0 (Thiazoles); 0 (alpha-Macroglobulins); 0 (amyloid beta-protein (1-40)); 0 (amyloid beta-protein (1-42))

L5 ANSWER 12 OF 12 MEDLINE on STN

AN 85239836 MEDLINE

DN PubMed ID: 4010500

TI Immunotactoid glomerulopathy.

AU Korbet S M; Schwartz M M; Rosenberg B F; Sibley R K; Lewis E J

SO Medicine; analytical reviews of general medicine, neurology, psychiatry, dermatology, and pediatrics, (1985 Jul) 64 (4) 228-43.
Journal code: 2985248R. ISSN: 0025-7974.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198508

ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850821

AB We present 11 patients with immunotactoid glomerulopathy, a new **syndrome** characterized clinically by proteinuria (11/11), microscopic hematuria (9/11) and hypertension (9/11). The patients consisted of six females and five males, aged 25 to 59 years (mean, 44.6). Proteinuria was the presenting feature and the reason for renal biopsy in all patients. The diagnosis of immunotactoid glomerulopathy was established at renal biopsy by the presence of glomerular extracellular

Entered Medline: 19980410

AB We have used the yeast two-hybrid system to isolate cDNAs encoding proteins that specifically interact with the 42-aa beta-amyloid peptide (Abeta), a major constituent of senile plaques in Alzheimer's disease. The carboxy terminus of alpha2-macroglobulin (alpha2M), a proteinase inhibitor released in response to inflammatory stimuli, was identified as a strong and specific interactor of Abeta, utilizing this system. Direct evidence for this interaction was obtained by co-immunoprecipitation of alpha2M with Abeta from the yeast cell, and by formation of SDS-resistant Abeta complexes in polyacrylamide gels by using **synthetic** Abeta and purified alpha2M. The association of Abeta with alpha2M and various purified amyloid binding proteins was assessed by employing a method measuring protein-protein interactions in liquid phase. The dissociation constant by this technique for the alpha2M-Abeta association using labeled purified proteins was measured (Kd = 350 **nM**). Electron microscopy showed that a 1:8 ratio of alpha2M to Abeta prevented fibril formation in solution; the same ratio to Abeta of another acute phase protein, alpha1-antichymotrypsin, was not active in preventing fibril formation in vitro. These results were corroborated by data obtained from an in vitro **aggregation** assay employing Thioflavine T. The interaction of alpha2M with Abeta suggests new pathway(s) for the clearance of the soluble amyloid peptide.

CT *Amyloid beta-Protein: ME, metabolism
Biotinylation
DNA, Complementary
Hela Cells
Humans
Neurofibrils
*Peptide Fragments: ME, metabolism
Precipitin Tests
*Protease Inhibitors: ME, metabolism
Protein Binding
Thiazoles
alpha-Macroglobulins: GE, genetics
*alpha-Macroglobulins: ME, metabolism

RN **2390-54-7 (thioflavin T)**

CN 0 (Amyloid beta-Protein); 0 (DNA, Complementary); 0 (Peptide Fragments); 0 (Protease Inhibitors); 0 (Thiazoles); 0 (alpha-Macroglobulins); 0 (amyloid beta-protein (1-40)); 0 (amyloid beta-protein (1-42))

L5 ANSWER 12 OF 12 MEDLINE on STN

AN 85239836 MEDLINE

DN PubMed ID: 4010500

TI Immunotactoid glomerulopathy.

AU Korbet S M; Schwartz M M; Rosenberg B F; Sibley R K; Lewis E J

SO Medicine; analytical reviews of general medicine, neurology, psychiatry, dermatology, and pediatrics, (1985 Jul) 64 (4) 228-43.
Journal code: 2985248R. ISSN: 0025-7974.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198508

ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850821

AB We present 11 patients with immunotactoid glomerulopathy, a new **syndrome** characterized clinically by proteinuria (11/11), microscopic hematuria (9/11) and hypertension (9/11). The patients consisted of six females and five males, aged 25 to 59 years (mean, 44.6). Proteinuria was the presenting feature and the reason for renal biopsy in all patients. The diagnosis of immunotactoid glomerulopathy was established at renal biopsy by the presence of glomerular extracellular

microtubules composed of immune reactants. All the biopsies studied by immunofluorescence (10 cases) had glomerular deposits of IgG and C3. In three biopsies studied with IgG subclass specific antisera, only one patient had monoclonal immunoglobulin deposits (IgG3 kappa). In six cases the glomerular deposits were analyzed for light chains. In three the deposits contained kappa only, and three consisted of both kappa and lambda. In two cases the immune **aggregates** were confined to the mesangium, and in the remaining eight cases, the deposits were present in the mesangium and the glomerular basement membranes. Electron-dense deposits composed of microtubules were present in the same distribution within the glomerulus as the immune reactants. The microtubules had a uniform diameter in each biopsy, but they varied in size from case to case. They were approximately the same size in eight cases (mean, 22.3 +/- 3 [SD] **nm**). Three cases had much larger microtubules: 34.2 **nm**, 35.4 **nm**, and 48.9 **nm** in diameter.
Although the 22.3-**nm** microtubules resembled amyloid in their appearance, glomerular distribution and random orientation in the tissue, they were more than twice the diameter of amyloid (8.9 **nm**), and Congo red and **thioflavin T** stains for amyloid were negative. Similar microtubular structures have been described in patients with cryoglobulinemia, SLE and paraproteinemia, but these diseases were excluded in our patients on clinical, serologic and in some cases histologic grounds. More important, none of our patients had clinical or histochemical evidence of amyloidosis, an entity which may be confused with immunotactoid glomerulopathy on a morphologic basis. Follow-up, from 22 to 94 months (mean, 52.6) was obtained in all 11 patients, and 2 clinical courses were noted. Six patients had progressive deterioration of renal function, with five requiring dialysis. This group had severe hypertension (4/6) and nephrotic-range proteinuria (5/6) at some point in their course. The remaining five patients with stable renal function had proteinuria of less than 2.0 g/24 hr in most cases (4/5), and none had severe hypertension. This dichotomy correlated with the distribution of immunotactoids.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Female; Male
Adult
Amyloidosis: PA, pathology
Basement Membrane: UL, ultrastructure
Creatinine: BL, blood
Cryoglobulins: AN, analysis
Glomerular Mesangium: PA, pathology
Glomerular Mesangium: UL, ultrastructure
Hematuria: PA, pathology
Humans
*Kidney Diseases: PA, pathology
*Kidney Glomerulus: PA, pathology
Kidney Glomerulus: UL, ultrastructure
Microscopy, Electron
Microscopy, Fluorescence
Microtubules: UL, ultrastructure
Middle Aged
Proteinuria: PA, pathology

RN 60-27-5 (Creatinine)

CN 0 (Cryoglobulins)

=>

Connection closed by remote host

microtubules composed of immune reactants. All the biopsies studied by immunofluorescence (10 cases) had glomerular deposits of IgG and C3. In three biopsies studied with IgG subclass specific antisera, only one patient had monoclonal immunoglobulin deposits (IgG3 kappa). In six cases the glomerular deposits were analyzed for light chains. In three the deposits contained kappa only, and three consisted of both kappa and lambda. In two cases the immune **aggregates** were confined to the mesangium, and in the remaining eight cases, the deposits were present in the mesangium and the glomerular basement membranes. Electron-dense deposits composed of microtubules were present in the same distribution within the glomerulus as the immune reactants. The microtubules had a uniform diameter in each biopsy, but they varied in size from case to case. They were approximately the same size in eight cases (mean, 22.3 +/- 3 [SD] **nm**). Three cases had much larger microtubules: 34.2 **nm**, 35.4 **nm**, and 48.9 **nm** in diameter.
Although the 22.3-**nm** microtubules resembled amyloid in their appearance, glomerular distribution and random orientation in the tissue, they were more than twice the diameter of amyloid (8.9 **nm**), and Congo red and **thioflavin T** stains for amyloid were negative. Similar microtubular structures have been described in patients with cryoglobulinemia, SLE and paraproteinemia, but these diseases were excluded in our patients on clinical, serologic and in some cases histologic grounds. More important, none of our patients had clinical or histochemical evidence of amyloidosis, an entity which may be confused with immunotactoid glomerulopathy on a morphologic basis. Follow-up, from 22 to 94 months (mean, 52.6) was obtained in all 11 patients, and 2 clinical courses were noted. Six patients had progressive deterioration of renal function, with five requiring dialysis. This group had severe hypertension (4/6) and nephrotic-range proteinuria (5/6) at some point in their course. The remaining five patients with stable renal function had proteinuria of less than 2.0 g/24 hr in most cases (4/5), and none had severe hypertension. This dichotomy correlated with the distribution of immunotactoids.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Female; Male
Adult
Amyloidosis: PA, pathology
Basement Membrane: UL, ultrastructure
Creatinine: BL, blood
Cryoglobulins: AN, analysis
Glomerular Mesangium: PA, pathology
Glomerular Mesangium: UL, ultrastructure
Hematuria: PA, pathology
Humans
*Kidney Diseases: PA, pathology
*Kidney Glomerulus: PA, pathology
Kidney Glomerulus: UL, ultrastructure
Microscopy, Electron
Microscopy, Fluorescence
Microtubules: UL, ultrastructure
Middle Aged
Proteinuria: PA, pathology

RN 60-27-5 (Creatinine)
CN 0 (Cryoglobulins)

=>
Connection closed by remote host